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Review

Osteoarthritis phenotypes and novel therapeutic targets

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ABSTRACT

The success of disease-modifying osteoarthritis drug (DMOAD) development is still elusive. While there have been successes in preclinical and early clinical studies, phase 3 clinical trials have failed so far and there is still no approved, widely available DMOAD on the market. The latest research suggests that, among other causes, poor trial outcomes might be explained by the fact that osteoarthritis (OA) is a heterogeneous disease with distinct phenotypes. OA trials might be more successful if they would address and target a specific phenotype.

The increasing availability of advanced techniques to detect particular OA characteristics expands the possibilities to distinguish between such potential OA phenotypes. Magnetic resonance imaging is among the key imaging techniques to stratify and monitor patients with changes in bone, cartilage and inflammation. Biochemical markers have mainly used as secondary parameters and could further delineate phenotypes. Moreover, post-hoc analyses of trial data have suggested the existence of distinct pain phenotypes and their relevance in the design of clinical trials.

Although ongoing work in the field supports the concept of OA heterogeneity, this has not yet resulted in more effective treatment options. This paper reviews the current knowledge about potential OA phenotypes and suggests that combining patient clinical data, quantitative imaging, biochemical markers and utilizing data-driven approaches in patient selection and efficacy assessment will allow for more successful development of effective DMOADs.

1. Introduction

Conservative estimates state that up to 240 million people around the world suffer from osteoarthritis (OA) [1]. On average, people begin experiencing OA symptoms at the age of 55 years and live 26 years with the symptoms [2,3]. OA decreases mobility, quality of life and productivity and increases morbidity, use of healthcare services and social expenditure [4]. Altogether, OA poses a large and very significant individual and societal burden [5]. Moreover, due to the ever-expanding ageing population together with the increasing levels of sedentary behavior and the diminishing levels of physical activity that are fueling the current obesity pandemic, the prevalence of chronic OA is expected to increase further and become established as the most common form of musculoskeletal disease by 2040.

Although the socioeconomic impact of OA is clear, existing therapeutic options are very limited and what is available is modestly effective at best in most patients. Huge efforts have been put into developing more effective and/or disease modifying treatments.

Disease modifying OA treatments, by definition, are able to positively influence both the structural as well as symptomatic disease course. A variety of potential disease modifying OA drugs (DMOADs) have been suggested to be effective in preclinical and early clinical studies but failed to reach structural and clinical endpoints in phase 3 clinical trials. A number of factors have been hypothesized to underlie this disappointing outcome. One of them supposedly is that OA is a heterogeneous disease, consisting of distinct subtypes, or phenotypes, while preclinical OA models typically test a particular OA pathogenic mechanism (e.g., mechanical instability, synovitis, or cartilage

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damage).

OA phenotypes can be defined as subtypes of OA that share distinct underlying pathobiological and pain mechanisms and their structural and functional consequences. As therapeutic interventions usually target just one or a few disease mechanisms, they might not be equally effective for all phenotypes. Consequently, any disease-modifying ability of an intervention in subgroups of trial populations might be diluted by the lack of efficacy in others. Also, representative outcome measures for efficacy might be different between OA phenotypes. Thus, the positive effect on radiographic joint space narrowing on standardized joint radiographs, the current "gold standard" that is currently required by regulatory agencies to qualify an agent as a DMOAD might not suffice for all phenotypes.

When one or more OA phenotypes are validated, every OA patient could be assessed for one or more parameters that characterize each of these phenotypes. Patients could classify for one or more phenotypes at the same time. This could help predict the future structural and/or clinical disease course (i.e. prognosis) and define potentially effective therapeutic targets in patients at high risk for disease progression.

Various imaging-based scoring systems and quantitative image assessment methodologies have been used to study OA phenotypes, primarily using conventional radiography or magnetic resonance imaging (MRI) and to a lesser degree ultrasound, computed tomography (CT) and nuclear medicine approaches that provide different means to characterize both structural and compositional changes in different joint tissues affected by OA. In trials, primarily radiography and/or MRI are used to support patient selection and disease modification claims for novel therapeutic agents. Fig. 1 illustrates examples of various imaging techniques that are used in OA studies.

Also, biochemical and -omics markers (biomarkers) have been proposed as phenotyping tools, although there are limited number of studies published on the topic. Most biomarker studies are focused on association with or correlation with disease stage or progression. Nevertheless, biomarkers measured in blood or urine may provide information on disease activity through measures of inflammatory burden (e.g. cytokine profiles), metabolic status (e.g. metabolomics), risk of disease (e.g. genomics) and tissue health (e.g. extracellular matrix turnover) [6,7].

The concept of OA heterogeneity and phenotypes is rapidly gaining acceptance and a growing number of researchers, initiatives and studies focus on or around this subject. In the current article, we will review work that has been done in OA phenotyping and how this might impact OA research and care. The focus will be on work that relates to or could positively impact therapeutic innovation and the scope will be limited to pharmacological interventions.

1.1. Conventional methods for phenotype definition

Most conventional methods for defining OA phenotypes distinguish between the primarily or predominantly affected joint tissue(s), e.g. articular cartilage, bone, osteophytes, bone marrow and/or synovial tissue and/or distinguish between patients with and without a particular characteristic, such as an increased infrapatellar fat pad signal intensity, high levels of a particular set of biochemical markers or a decreased pain pressure threshold. The phenotypes that have more symptoms and/or a worse prognosis (i.e. a need for treatment) may offer a specific target for intervention and are the most interesting from the therapeutic point of view.

1.1.1. Potential bone phenotypes

Although the general consensus is that bisphosphonates are ineffective for reducing pain and structural progression in unselected knee OA patients [8], bone marrow lesions (BMLs) on MRI have received much interest over the last years, especially when testing new molecules such as anti-interleukin-1 antibodies in synovitis-associated OA and bisphosphonates [9].

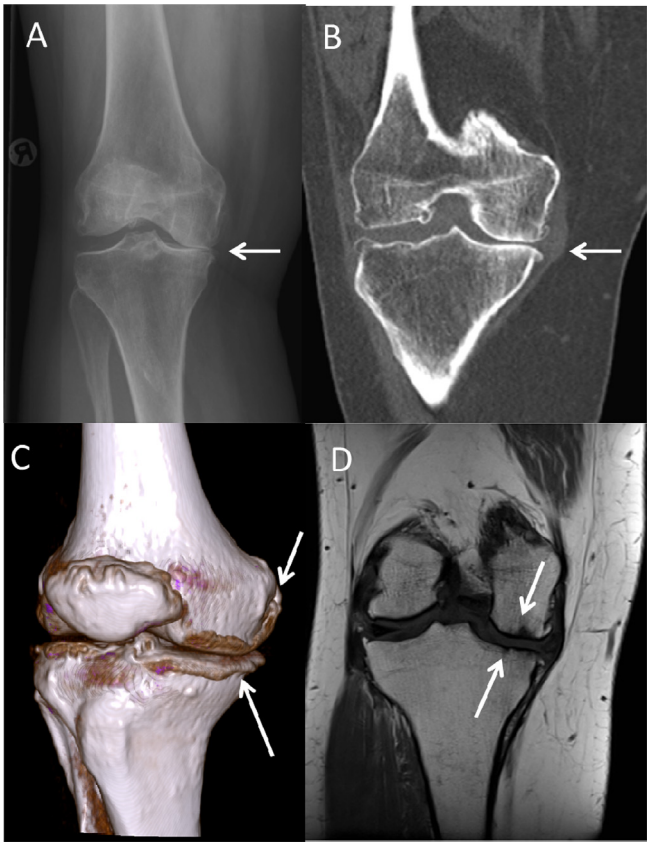

Fig. 1. Examples of various imaging technologies used in osteoarthritis (OA) studies, using imaging results of a 57-year-old female with knee OA and a painful and swollen knee. *A) Conventional standing semiflexed radiograph of the right knee, showing severe medial knee OA. B) Computed tomography (CT) scan of the same knee, showing in more detail the kissing bone, osteophytes at the medial and lateral joint margins and the tibial eminentia as well as subchondral sclerosis and meniscal extrusion (arrow). C) 3D volume rendering of the CT scan, allowing to study the bony morphology in 3D. It becomes apparent that osteophytes are made up of a bony rim enlargement from the edges of both tibia and femur (arrows). D) Coronal T1 weighted magnetic resonance imaging without fat saturation of the same knee, now also showing small hypointense bone marrow lesions in the medial femur and tibia (arrows).*

BMLs appear as ill-defined signal intensity changes in the subchondral bone that are hypointense on T1 weighed MR images and hyperintense on fluid-sensitive images with fat saturation, i.e. T2 images, proton-weighted and fat-saturated images and/or short-TI inversion recovery (STIR) images. Fig. 2 shows an advanced MRI sequence, known as dynamic contrast enhanced (DCE)-MRI, where images are acquired over a period of 3–5 min after the injection of a gadolinium (Gd) based contrast agent. The images show the rate of Gd absorption by soft tissues or tissue lesions, such as synovial tissue and bone lesions. Once DCE-MRI is processed using specialist software packages, a color overlay is displayed on grey-scale MRI, facilitating the visual and quantitative assessment of the volume and severity of BMLs and synovitis [10].

BMLs scored on static fluid-sensitive MRI sequences are positively associated with symptoms and disease progression in knee OA [11,12]. They also suggest a phenotype of knee OA patients with particular involvement of the subchondral bone in the disease process. Moreover, this subchondral process might be amenable to agents that are readily available from the osteoporosis field. Laslett et al. performed the quintessential trial (ZAP1) on this subject by demonstrating that a single gift of 5 mg zoledronic acid in 59 patients with knee OA with BMLs reduced the visual analogue score (VAS) for pain and areal BML size at 6 months as compared to placebo infusion [13]. The effects on

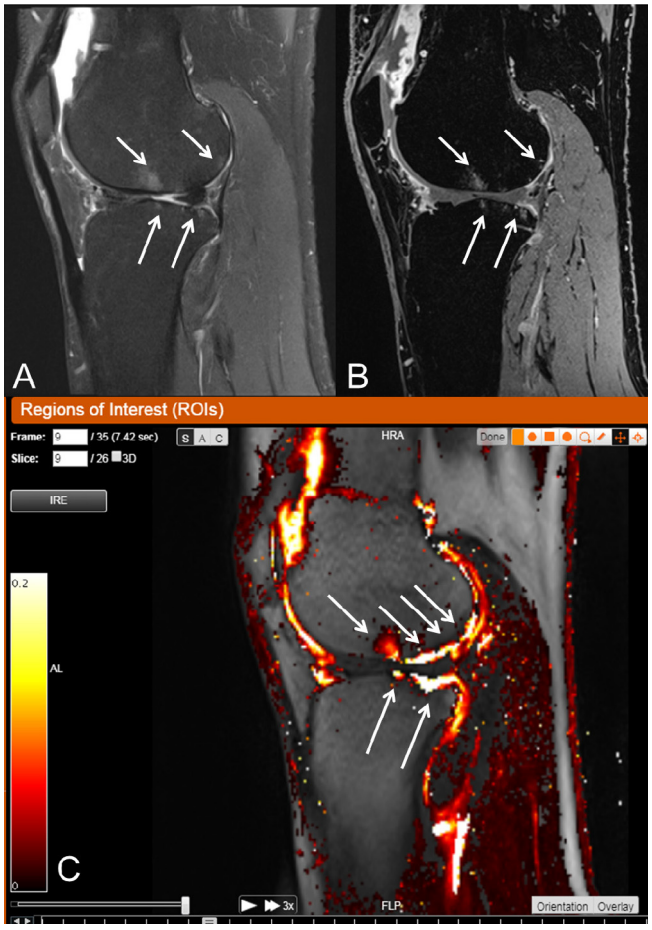

Fig. 2. Magnetic resonance imaging (MRI) of bone marrow lesions (BMLs) in knee osteoarthritis. *These images were acquired from the same patient as in* Fig. 1. *A) Proton density weighted MRI. Arrows point to the small ill-defined BMLs in femur and tibia. Note the moderate effusion/synovitis in the suprapatellar pouch in the upper part of the image. Most of the increased signal intensity corresponds to contrast enhancing synovium in the suprapatellar pouch. B) 3D VIBE sequence with fat saturation. Enhancement of the same BMLs in both femur and tibia with a similar size. C) Dynamic contrast enhanced MRI. High perfusion in the same BMLs as in A and B. However, in addition, there is a visible high enhancement of the subchondral bone in both femur and tibia that is not visible on the static images in A and B.*

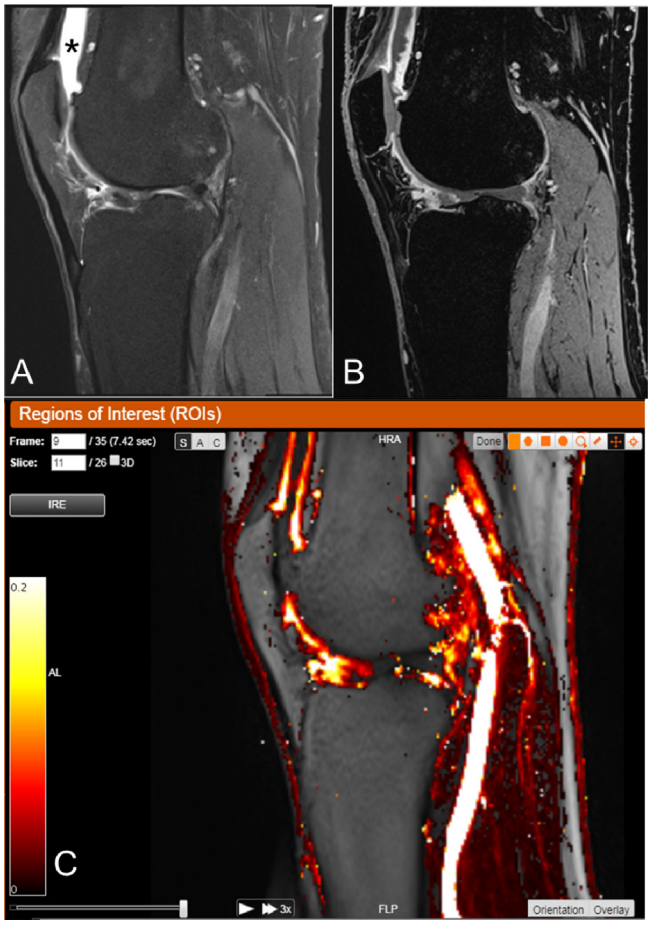

Fig. 3. Magnetic resonance imaging (MRI) of synovitis and effusion in knee osteoarthritis. *These images were acquired from the same patient as in* Figs. 1 and 2. *A) Proton density weighted sagittal image through the mid-part of the knee, showing moderate effusion/synovitis in the suprapatellar pouch in the upper part of the image (*) as well as an increased signal intensity in Hoffa's fat pad. B) Post contrast gradient echo 3D VIBE sequence with fat saturation, showing increased enhancement of an irregular thickened synovium of the suprapatellar pouch. Note the hypointense area inside the enhancing synovium which corresponds to effusion, the enhancing synovium on the inside of Hoffa's fat pad and the slight enhancement in the posterior capsule. C) Dynamic contrast enhanced MRI with the color map of the initial rate of enhancement, the most severe inflammation is shown in white-bright yellow and lower degrees of inflammation in red colors. The image shows spotted areas of high perfusion in the synovial membrane in the suprapatellar pouch, high uniform enhancement of the synovium covering Hoffa's fat pad and slow enhancement in the posterior capsule. This reflects different perfusion patterns of the various tissues that could serve as specific inflammatory phenotype profiles.*

pain and BML size abated at 12 months. After these encouraging results, a multicenter, randomized, double-blind, placebo-controlled trial (ZAP2) was performed to determine the effect of two annual infusions of zoledronic acid on pain. This time also the cartilage volume was measured at 24 months in 223 knee OA patients with BMLs [14]. The results of ZAP2 have so far been presented in abstract format only, but were less promising than for ZAP1 [15]. It appeared that knee pain and function and BML size at 24 months in actively treated patients were not statistically significantly different from patients that were administered placebo. We note that the effects of zoledronic acid did seem more prominent in a pre-specified subgroup of patients without radiographic knee OA. The final and complete results of ZAP2 are eagerly awaited and other trials of zoledronic acid or similar agents in knee OA patients with BMLs are underway, including COAST-1 and ZODIAK trials. Other bone-active agents might also be of interest in this respect. A sub-analysis of the SEKOIA trial suggested that treatment with strontium ranelate was able to reduce cartilage volume loss in patients with knee OA with BMLs as compared to placebo [16]. Moreover, a positive association between an increase in BML size and cartilage volume loss was observed in the placebo group, but not in patients that were treated with strontium ranelate, 1 or 2 gr/day.

1.1.2. Potential inflammatory phenotypes

Synovitis, usually low-grade, is a common OA feature and could be amenable to the wide range of anti-inflammatory agents that are available for inflammatory rheumatic diseases. Commonly applied imaging techniques for the identification and quantification of synovitis are ultrasound (US) and MRI. MRI synovitis may manifest itself as a thickened and contrast-enhancing synovial membrane and/or indirectly as joint effusion and increased signal of a thickened synovium on a fluid sensitive sequence (Fig. 3). When it comes to quantifying synovitis, it is critical to use Gd based contrast agents as only the contrast enhanced images differentiate effusion and synovium, thus allowing for precise quantification of synovitis.

Hand OA, in particular the erosive form of hand OA is commonly considered an inflammatory OA phenotype and seems to be an obvious target for anti-inflammatory treatment. A number of anti-inflammatory agents have been tested for efficacy in hand OA patients and US is a

relatively inexpensive and accessible tool to detect inflammation in these patients. Several recently published studies have found that US based inflammatory signs in erosive hand OA [17–19] can predict erosive progression [20]. The EHOA trial is a recently published one-year, double-blind, randomised, placebo-controlled, multicenter trial in 90 patients with symptomatic, erosive and inflammatory hand OA [21]. Synovitis was assessed clinically and with US Power Doppler in all patients and with MRI in a patient subset. Included patients were required to be non-responsive to a stable dose of non-steroidal anti-inflammatory agents. Etanercept® was dosed as 50 mg/week for the first 24 weeks and as 25 mg/week for the rest of the year. The visual analogue scale (VAS) for pain and other clinical outcomes favored Etanercept® over placebo, but differences were not statistically significant. the trial showed that the joint 'remodeling' was higher in the Etanercept® group and in joints with soft tissue swelling and/or power Doppler signal in particular (i.e. positive statistical interaction). MRI synovitis scores at one year did not differ between study arms, but BML scores decreased more in the Etanercept® treated patients. Again, the response was stronger in patients with MRI-detected synovitis.

The HUMOR trial followed a relatively similar approach and treated 43 symptomatic, erosive and inflammatory hand OA patients with Adalimumab®, 40 mg every other week, or placebo [22]. Synovitis was assessed by MRI. No difference in pain was observed after 12 weeks. Correspondingly, changes in synovitis and BML were small and similar between study arms.

Synovitis is a feature of knee OA in substantial numbers of patients and might even predate knee OA in some [23] (Fig. 3). It is associated with pain and structural progression [23,24]. Lutikizumab® (ABT-981), an anti–interleukin-1 alpha/beta dual variable domain immunoglobulin, was recently tested in a one-year, phase 2 trial in knee OA patients with evidence of synovitis on ultrasound or MRI [25]. Lutikizumab® was administered subcutaneously, every other week, in doses of either 25, 100, or 200 mg. Lutikizumab® met the primary endpoint of reduction in WOMAC pain at 16 weeks compared with placebo at the dose of 100 mg, but not at 25 mg or 200 mg and not at the other time points. Cartilage thickness, synovitis and other structural endpoints both on MRI and radiographs were similar between Lutikizumab® and placebo. Several biomarkers reflecting tissue inflammation were measured in the two phase I studies, showing that these were modulated in a dose-dependent way, indicating that select biomarkers could reflect tissue inflammation complementary to imaging. Biomarker data from the phase II study have not been published.

One other interesting trial of intra-articular glucocorticoid injection in 97 symptomatic hip OA patients quantified effusion-synovitis in the index joint using ultrasound and MRI at baseline and 8 weeks post-injection [26]. The group as a whole showed clinical improvement in this non-placebo-controlled study, but, surprisingly, baseline measures of effusion-synovitis did not differ between responders and non-responders according to a variety of definitions. Although these data might question the existence and/or relevance of an inflammatory hip OA phenotype, it should be noted that none of the effusion-synovitis measures changed from the injection. So, alternatively, this might indicate that the measures for effusion-synovitis were not optimal for this purpose.

1.1.3. Biochemical markers

Biochemical markers have the potential to add to the information that can be obtained from imaging modalities, as they might serve as dynamic measures of low-grade inflammation and/or metabolic alterations associated with some forms of OA. Biochemical markers in blood and urine do, however, lack specificity for the index joint(s) and are subject to multiple potential sources of background noise. Instead biochemical markers may provide measures of disease activity on a systemic level. It has been suggested that progression of disease happens in intervals, thus biochemical markers may be attractive for patient monitoring and for finding the timepoint where imaging assessment should be conducted. In addition, one could imagine that biochemical marker as monitoring tool could be used to identify turning points and change in phenotypes during the course of disease development; for example change from a phenotype without bone involvement to a phenotype with bone involvement [27]. Biochemical markers in synovial fluid are more specific for the index joint, but their measurement is not standardized and requires relatively invasive arthrocentesis, which is often impractical from the perspective of clinical trial design and patient retainment.

Some studies have attempted to distinguish between potential phenotypes based on biochemical characteristics. One study assessed high-sensitivity C-reactive protein, (hsCRP) and an MMP-derived degradation fragment of C-reactive protein, CRPM, as a marker of more chronic tissue inflammation in serum of primary knee OA patients. They observed patients without increased hsCRP or CRPM levels (69%), with only an increased hSCRP level (12%), with only an increased CRPM level (13%), or with both increased hsCRP and CRPM levels (6%). These subsets differed with regard to gender, body mass index, radiographic knee OA severity and serum levels of MMP-derived neoepitopes of collagen type 1, 2 and 3 (C1M, C2M and C3M, respectively) [28]. Likewise, serum levels of C1M, C2M, C3M and CRPM and erythrocyte sedimentation rate (ESR) were assessed in Cohort Hip & Cohort Knee (CHECK), a cohort of persons with early-stage symptomatic primary knee and/or hip OA. Principal component analysis again suggested that CRPM and C3M may reflect different inflammatory domains than do hsCRP, ESR and C1M [29]. The potential relevance and implications of these findings remain to be determined.

A recent study also illustrated that the driving inflammatory pathways in the OA process may differ between knee and hip. It appeared that cytokines were differentially present in serum and synovial fluid between knee and hip OA patients [30].

Biochemical markers have also been used as secondary outcome parameters in OA trials. Although marker levels seem to be associated with the efficacy of tested interventions in a number of studies, they do not in others [31]. It is not always clear how such findings are to be interpreted. In contrast, biochemical markers are obvious choice for target engagement and pharmacodynamic markers. Such data may provide link between the drug mode of action and efficacy, as well as insight to the phenotypic differences between responding and non-responding patients. In other word, biochemical markers may through DMOAD trials provide clue to the underlining mechanisms to different phenotypes. Moreover, there is potential for combining imaging and biochemical markers to develop combination markers.

1.1.4. Potential pain phenotypes

Pain phenotyping might also be relevant for DMOAD interventions, as is illustrated by recent phase 2a and 2b trials of the Wnt pathway inhibitor SM0460. In the phase 2a trial, 455 symptomatic and radiographic knee OA patients were administered a single, intra-articular injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo [32]. Pain and function improved at all time points in all study arms, including the placebo arm, according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index. At 52 weeks, in a prespecified unilateral symptomatic subgroup, the 0.07 mg dose group showed significant improvements in WOMAC pain and clinically meaningful and significant improvements in WOMAC function compared to placebo. In a post-hoc subgroup with unilateral symptoms and without widespread pain, the 0.07 mg dose group showed both clinically meaningful and significant improvements in WOMAC pain and function compared to placebo at weeks 39 and 52, respectively. Widespread pain was assessed by the Widespread Pain Index and Symptom Severity Score. Radiographic joint space narrowing over 1 year as compared to placebo was decreased in the 0.07 mg dose group and in patients with unilateral symptoms only (with or without widespread pain).

The phase 2b study included 695 knee OA patients with unilateral

symptoms only [33]. The results from this study confirmed the previous finding that WOMAC and the numeric rating scale (NRS) for pain, WOMAC physical function and patient global assessment were improved at 12 and/or 24 weeks in the 0.07 and 0.23 mg dose groups as compared to placebo.

Interestingly, a post-hoc analysis of the placebo groups of two phase 3 trials of oral salmon calcitonin for knee OA showed that pain was reduced more in the composite of questions related to weight-bearing pain compared to non-weight-bearing pain of the target knee, suggesting distinct categories of pain [34]. Likewise, one study suggests that associations of inflammatory mediators might differ between pain at rest and on movement [35].

Structural abnormalities and pain often correlate poorly. Imaging findings and pain have been poorly linked in the past, especially when using conventional radiographs that only show the late-stage bony changes from OA and thus tells more about the patients OA history than the current clinical status. Another big confounder for the missing link between structural joint changes and pain is the inherent nature of OA pain as remitting relapsing compared to the continuous slow progression of degenerative tissue changes with limited or no reversibility. BMLs, synovitis and effusion are considered inflammatory markers and have been linked to faster progression of both radiographic OA as well as cartilage destruction on MRI. MRI detected synovitis can be seen in more than 50% of patients with OA [36] and higher degrees of synovitis is associated with more severe pain [24] as well as higher levels of systemic and synovial pro-inflammatory cytokines [37,38]. This might be the pain link as some of these cytokines (i.e IL-6) are known to sensitize peripheral nerve-endings [39].

DCE-MRI has also been used to study synovitis and joint inflammation in knee OA, where high correlations between DCE-MRI markers of increased perfusion and histological synovial biopsies were found [40]. In addition, higher correlations between DCE-MRI markers of perfusion and Knee injury and Osteoarthritis Outcome Score (KOOS) pain scores have also been found in both the synovium [41] and Hoffa's fat pad [42] compared to conventional static MRI measures of synovitis on both non-contrast and contrast enhanced MRI sequences, suggesting that DCE-MRI might be the method of choice to find specific inflammatory phenotypes linked to specific cytokine profiles, histology, pain severity and pain responses.

1.2. Novel methods and approaches for phenotype definition

The data above partly supports the plausible concept of OA phenotypes that might each require different approaches in terms of diagnosis, treatment and prognosis. Yet, they also illustrate that the conventional methods for distinguishing between OA phenotypes might not suffice for complex diseases such as OA. Novel approaches to distinguish between OA phenotypes and identify therapeutic targets for these phenotypes are therefore of great interest and importance.

Synovial biopsies might also provide detailed information about the nature of the synovitis in OA and/or inflammatory arthritis and synovial biopsy could eventually be a useful tool in clinical trials [43,44]. One relatively small study showed increased expression of IL-17A in synovial biopsies from knee or ankle joints of OA patients similar to that in rheumatoid arthritis and psoriatic arthritis patients. Yet, it was also observed that expression of IL-17A, IL-17F and their receptors was highly variable between individual patients [45]. This might explain why some patients do respond to IL17 inhibitors and others do not, although this was not investigated in the current study. Although informative from a research perspective, the invasive synovial biopsy is unlikely to find its way to routine OA care anytime soon.

Imaging techniques that might also provide dynamic measures of tissue composition and/or function or characteristics of present inflammation might be of particular interest for phenotyping OA patients. Macrophages might play an important role in the synovitis in OA joints and as such are potential therapeutic targets. The folate receptor β (FR-β) is present on activated macrophages, but not on resting macrophages or other immune cells. The FR-β can be targeted by the folate receptor-specific molecular imaging agent etarfolatide (99mTc–EC20) for SPECT/CT. It was shown that 76% of the 50 knees of 25 people with radiographic and symptomatic OA in at least one knee were positive for activated macrophages in at least one joint region, with uptake observed in the joint capsule (immediately adjacent to the joint), synovium and/or subchondral bone. Moreover, etarfolatide uptake was associated with pain severity and radiographic OA parameters. Etarfolatide uptake was also observed in other joints, such as the finger joints, thumb bases, shoulders, big toes and ankles, and was associated with presence of pain in these joints as well [46]. To the best of our knowledge, no interventional studies using etarfolatide imaging as an outcome have been published so far.

There is increasing consensus that crystal deposition disease leading to accelerated OA is underdiagnosed in OA trials as only the late manifestations of the calcium pyrophosphate deposition disease and gout can be appreciated on conventional radiographs and small calcifications can be invisible on MRI. Novel imaging technologies such as dual energy CT and cone beam CT [47–49] with advanced dose reduction techniques can potentially aid in excluding crystal arthritis patients from many OA trials as these patients are likely to have a different pathogenesis.

Finally, continuous technological development of MRI might help enrich certain phenotypes for OA studies or map both structural and compositional changes in joint tissues. Fig. 4 gives examples of T2 MRI maps for non-contrast cartilage composition and diffusion weighted imaging and corresponding apparent diffusion coefficients (ADC) maps for synovial and bone marrow inflammation that can complement the static and dynamic perfusion MRI sequences.

"Omics" analysis of joint tissues such as cartilage, synovium and synovial fluid using targeted approaches can be used to identify candidate biomarkers and potential therapeutic targets, thus underpinning phenotyping and the development of future DMOADs [50]. However, most "omics" analyses have focused on the associations of particular molecules or molecular changes with OA presence, severity and rate of progression so far, rather than on phenotype discovery. Moreover, further integration with clinical and imaging data and validation studies has been advised to bring the "omics" field to its full potential and translate its findings to useful tools in clinical care [51].

There has been a significant explosion in big data science in the last decade. This development is revolutionizing the development of diagnostics and therapeutics, especially when combined with the aforementioned high-throughput "omics" techniques. Applying computational approaches to "big data" from "omics" platforms can facilitate the development of multiplex diagnostics for OA [52]. Comparative proteomics of alkaptonuria, which can lead to an extreme form of OA has already provided novel insights into inflammation and oxidative stress by revealing pathologically elevated levels of CRP and advanced oxidation protein products [53]. Including radio-omics with computer assisted analysis of imaging data into this equation should help enhance specific imaging phenotypes by i.e standardizing the analysis of joint space narrowing and Kellgren & Lawrence or OARSI grading on conventional radiographs [54], cartilage volume and thickness measurements from MRI [55], meniscal tear evaluation [56], synovial volume from static contrast enhancing MRI [57], synovial volume and perfusion characteristics from DCE-MRI [10,57] and/or bone volume from 3D MRI [58,59] or CT scans [60] (Fig. 1).

2. Discussion

OA phenotyping has the potential to make important and impactful contributions to the development of more effective and/or disease modifying interventions for OA. Knowledge of heterogeneity of the many aspects around OA would help refine the design of future trials of potential DMOADs, better define potential treatment targets, improve

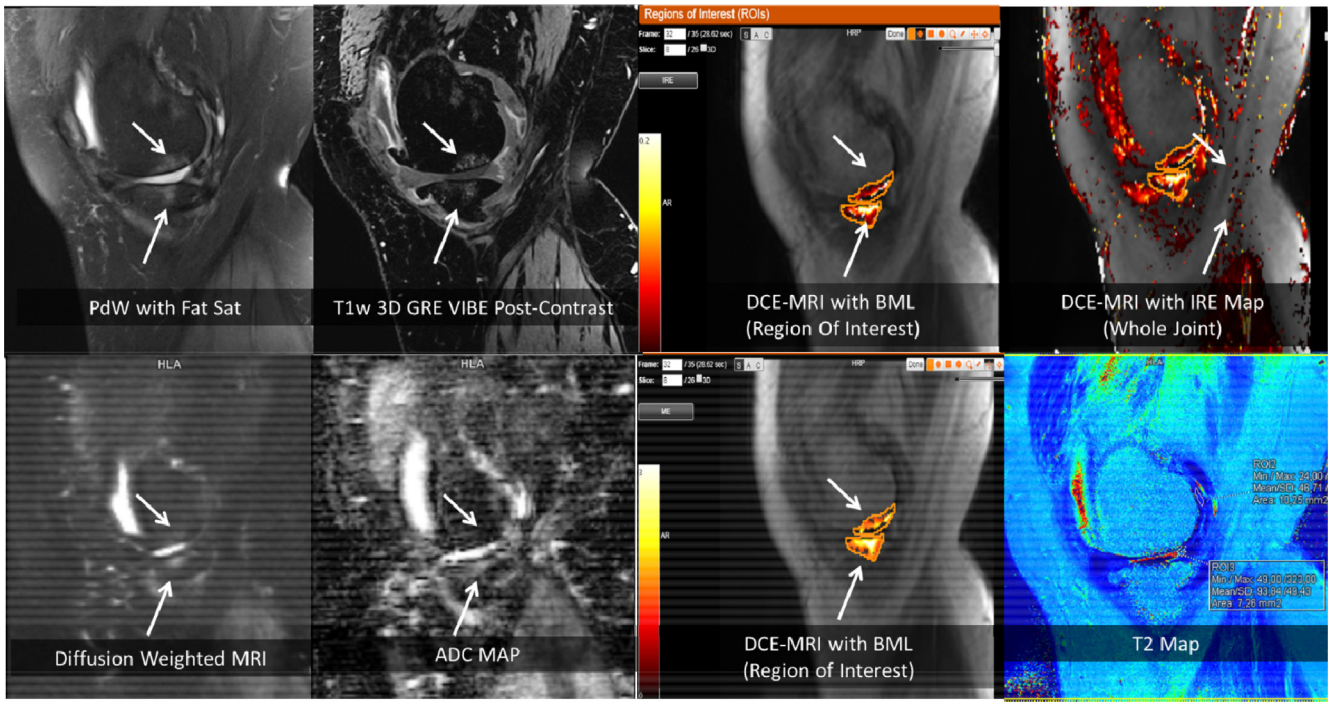

Fig. 4. Advanced MRI sequences and corresponding quantitative maps. Arrow points indicate the bone marrow lesion (BML) at all the different sequences. Top row, from left to right: proton density weighted (PdW) sagittal image, T1 weighted gradient Echo VIBE post-contrast image, dynamic contrast enhanced (DCE) MR image and the map of initial rate of enhancement (IRE), showing areas with more inflammation in white-yellow colors and the areas with less inflammation in red colors. Bottom row, from left to right: diffusion weighted MRI, corresponding apparent diffusion coefficient (ADC) map allowing quantification of cellular density and water diffusion, DCE-MRI with the map of maximum enhancement showing areas with much perfusion in white-yellow colors and areas of less perfusion in red colors, and lastly, the T2 map showing cartilage composition. Note that the BML seen on the static and DCE-MRI sequences is not depicted on the diffusion map. On the other hand, the increased signals in the tibial plateau on the diffusion weighted sequence and the ADC maps reflect increased water diffusion, corresponding to a higher degree of perfusion (yellow colors) on the DCE-MRI sequences which might indicate a specific BML phenotype. This warrants more research. Also note that the T2 image shows high T2 values around 90 ms in the cartilage adjacent to areas of denuded cartilage (red colors), while the ROI in the posterior part of the femoral condyle has near-normal values around 46 ms.

the ability to select appropriate patients for the tested intervention and to adapt outcome measures to the situation.

There is a need to effectively combine parameters that correspond to different domains that might be relevant for OA phenotyping, including measures for cartilage quality, three-dimensional bone morphology, subchondral bone metabolism, inflammation and others into an interpretable multi-parametric assessment. Ideally, these parameters are easy and cheap to collect, also in clinical care. Nevertheless, in the research stage, more specialized and/or complex methods might also be useful to come to an OA phenotype classification.

Most current studies into OA phenotypes are focused around knee OA [61]. OA driving mechanisms might, however, very well differ between joints [30,62]. More research into other joints, such as the hips and spine, is therefore to be encouraged.

Collaborations between different types of researchers in the OA field will be particularly important for phenotype studies. To effectively distinguish between phenotypes, data from different OA domains might be needed (e.g. imaging, pain assessment, motion analyses, biochemical markers, omics data) and researchers from each of these fields could provide important knowledge and expertise. Moreover, some approaches will require complex statistical and computational analyses so that statisticians, data scientists and computational scientists might prove indispensable. Finally, the OA phenotype research field could also benefit from knowledge that has been obtained from efforts to phenotype other diseases.

Data on potential phenotypes might come from both preclinical and clinical studies. Both observational (e.g., trajectory analyses) and interventional studies (e.g., characterizing responders vs. non-responders or studies in particular OA subtypes only) can be useful. Clinical studies typically are, however, relatively expensive and organizationally complex as compared to preclinical studies and this might be true all the more for clinical studies to be of use for phenotype analyses. Typically, they will then require more subjects and parameters to sufficiently cover different phenotypes and/or longer follow-up times to distinguish between trajectories or compare outcomes between phenotypes. Combining basic patient information, functional imaging and carefully selected panels of biochemical markers and omics data can help in achieving enhanced patient stratification and lead to better designed clinical trials [50] and enhance the ability to recruit the right patients for trials [63].

3. Conclusion

The existing literature points to numerous clues that OA phenotypes do actually exist. However, the OA phenotype research field is relatively new and as an emerging area it has not yet matured or led to any major discoveries with significant implications for the OA research field and clinical care so far. It would appear that the hard work in this area has yet to begin. Various international, US and EU based consortia have focused on the use of clinical, imaging and biochemical data to study disease progression in OA cohorts but very few studies have focused on OA phenotypes. We need more high-quality and better standardized data on the full spectrum of “omics” techniques and biochemical OA markers and then link these data with sensitive imaging parameters before we can develop combination biomarkers for different OA phenotypes. We need to assemble new panels of imaging and biochemical markers that can distinguish between distinct OA phenotypes and this can greatly facilitate drug development from early discovery to late

clinical development [6,7].This is going to be a very challenging but exciting and rewarding area of research activity in the future and should enable us to develop combination biomarkers that can be used to define and differentiate distinct OA phenotypes.

4. Declarations of interest

Olga Kubassova and Mikael Boesen are shareholders in Image Analysis Group and have received consultancy, speaker and travel fees from Image Analysis Group, Eli Lilly, Esaote, Celgene, Pfizer, Abbvie, Carestream/Canon, Siemens and AstraZeneca. Anne-Christine Bay-Jensen is an employee and shareholder of Nordic Bioscience. Ali Mobasheri is President-Elect of the Osteoarthritis Research Society International (OARSI), an employee of a government funded research institute in the Republic of Lithuania and a consultant to Image Analysis Group. Please see our completed ICMJE forms or Disclosure of Potential Conflicts of Interest for details.

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